REMARKS

Status of Claims

Prior to this Amendment, claims 1-44 were pending, with claims 6-9 and 17-44 being withdrawn from examination as being drawn to non-elected inventions. Thus, claims 1-5 and 10-16 were under examination. With this Amendment, claims 1, 12, 13, 17, 19 and 31 are being amended, and no claims are being canceled or added. Thus, following entry of this Amendment, claims 1-44 remain pending in the application, with claims 1-5 and 10-16 under examination. The various rejections raised in the Office Action are discussed in more detail below.

The Amendments of the Claims

Claim 1 has been amended with respect to sentence construction by deleting the semicolon ";" and inserting a comma ",".

Claims 12, 13, and 19 have been amended to correct obvious typographical errors.

Claim 17 has been amended to recite that the "glycyrrhizin is added in an amount such that the composition is substantially free of uncomplexed active agent" for clarity. Support is found in the specification at paragraph [0019].

Claim 31 has been amended with respect to sentence construction by deleting the semicolon ";" and inserting a period ".".

No new matter is added by virtue of the amendments. Entry is therefore respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-5 and 10-16 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over U.S. Patent No. 6,541,048 ("Zyck"). Applicants traverse the rejection.

Claim 1 recites a composition comprising a pharmaceutically acceptable carrier, an active agent having at least one nitrogen containing moiety, and glycyrrhizin in an amount such that the composition is substantially free of uncomplexed active agent. As described in the specification, glycyrrhizin appears to form a complex with the active agent, which results in increased solubility of the active agent.

Glycyrrhizin has been typically used as a flavoring agent or sweetener, and is generally present at 0.01-0.2% by weight.[1] In contrast to the typical use of glycyrrhizin as a sweetener, the claimed compositions not only comprise a complex of glycyrrhizin and the active agent, but have a sufficient amount of glycyrrhizin to complex with a substantial fraction of the active agent, thereby forming a composition substantially free of uncomplexed active agent.

The use of glycyrrhizin as a sweetener is exemplified in the reference of Zyck, cited by the Patent Office in rejecting the instant claims. Zyck discloses a chewing gum based composition for oral delivery of acid blocking agents, such as famotidine and ranitidine. The composition has a chewing gum core, which is covered with a coating formed of the acid blocking agent and a sweetener composed mainly of a bulk sweetener, including sugar and sugarless sweeteners. Bulk sweeteners listed as being suitable for forming the coatings include sucrose, dextrose, maltose, fructose, galactose, corn syrup solids, sorbitol, mannitol, xylitol, and maltitol.

Zyck also discloses that in some embodiments, *high intensity sweeteners* can be added *in addition to the bulk sweeteners* to "improve the taste of the finished product."[2] Zyck lists a number of high intensity sweeteners for this purpose, including "sucralose, aspartame, N-substituted APM derivatives, acesulfame, alitame, glycyrrhizin, dihydrochalcones, thaumatin, monellin, and the like, alone or in combination."[3] Specific examples given in Zyck describe

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[1] Specification, paragraph [0042].

[2] U.S Patent No. 6,541,048, column 5, lines 1-3.

[3] *Ibid*, column 7, lines 47-53.

coating mixture composed of bulk sweeteners , such as sugar, dextrose, and maltitiol. Where high intensity sweeteners are used, the specific examples recite acelsulfame K or aspartame, and in amount no greater than 0.3 weight %. In contrast, the amount of acid blocker in the compositions is 1 weight %, an amount that is substantially more than the amount of high intensity sweetener. Moreover, in some embodiments described in Zyck, the high intensity sweeteners are *encapsulated* to slow its release from the composition and thereby lengthen the period that the sweetener masks the taste of the active agent.[4]

The description in Zyck points out a number of points regarding the use of high intensity sweeteners with the acid blockers. First, it is used as an adjunct to the bulk sweeteners, and therefore represents only a minor portion of the composition. Second, the weight % of high intensity sweeteners is much lower than the weight % of active agent (*i.e.*, acid blocker), or otherwise limited in its ability to react with active agent because the high intensity sweetener is in an encapsulated form. Third, glycyrrhizin is not pointed out as having any advantageous or desirable properties as compared to other high intensity sweeteners when used with the acid blockers.

When rejecting the claims under 35 U.S.C. §103(a), the Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). *See* M.P.E.P. §2142. To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not

[4] *Ibid*, column 7, lines 53-56.

applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); *see also* M.P.E.P. §706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

In the instant case, Zyck fails to teach or suggest each and every limitation of the claimed compositions. Although Zyck suggests that glycyrrhizin may be used as a high intensity sweetener for masking any unpleasant taste of the active agent, there is no teaching or suggestion for use of glycyrrhizin in an amount sufficient to produce a composition that is substantially free of any uncomplexed active agent with a nitrogen-containing moiety. The basis of the rejection has focused on individual components of the claimed composition and in the process disregarded the requirement of considering the claim as a whole in determining obviousness. *See* M.P.E.P §2141.02. The rejection has failed to consider the use of glycyrrhizin in an amount sufficient to complex with the active agent containing the nitrogen-containing moiety to form a composition that is *substantially free of uncomplexed active agent*. Hence, Zyck does not teach or suggest each and every element of the claimed subject matter.

Moreover, although Zyck discloses individual components glycyrrhizin and active agent with a nitrogen containing moiety, there is no suggestion or motivation to modify the teaching of Zyck to arrive at the claimed compositions. Zyck fails to disclose or suggest any reason why glycyrrhizin would be advantageous or desirable amongst all the available high intensity sweeteners nor disclose or suggest any advantage or desirability of using it in an amount that is sufficient to complex the nitrogen containing active agent to produce a composition that is substantially free of uncomplexed agent. The picking and choosing amongst the components described in Zyck without pointing to some suggestion or motivation in the reference or common knowledge in the art to combine the elements is impermissible hindsight reconstruction. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *see also* M.P.E.P §2142. Nothing in Zyck or in the stated bases of the rejection is there any suggestion that at the filing date of the instant application it was within the knowledge of the ordinary person of skill in the art that glycyrrhizin increased the solubility of active agents containing a nitrogen moiety.

There is also no reasonable expectation of success. The teachings of Zyck in reference to glycyrrhizin is its use at an additive, *i.e.*, as a sweetening agent to mask the flavor of the acid blocking agent. As noted in the present disclosure, the use of glycyrrhizin as a sweetening agent is typically at about 0.1 to 0.2 weight %, an amount also suggested in Zyck. To extend the time period for the flavor masking effect, Zyck also suggests that the high intensity sweetener be provided in an *encapsulated* form, which would limit or prevent interaction of the high intensity sweetener with any active agent with a nitrogen containing moiety. In these circumstances, applicants submit that the amount and/or form of glycyrrhizin, if used, are insufficient to form a composition that is substantially free of uncomplexed active agent.

When Zyck is appropriately considered in its entirety, its teachings are fatally deficient and do not support a case of *prima facie* obviousness. For the reasons given, the rejection is in error, and withdrawal of the rejection is respectfully requested.

Claims 1-5 and 10-16 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over U.S. Patent No. 5,576,014 ("Mizumoto"). Applicants traverse the rejection.

Mizumoto discloses intrabuccally dissolving molded compositions for administration of an active agent. The molded compositions are made using a granulated mixture of a saccharide having low moldability and a saccharide having high moldability. Mizumoto describes use of artificial sweeteners *as an additive* and recites various sweeteners, including saccharin sodium, glycyrrhizin dipotassium, aspartame, stevia, and thaumatin. Mizumoto provides a number of exemplary molded compositions but the only artificial sweetener disclosed is aspartame, which is used at about 0.23 kg per 1.0 kg of famotidine (Example 10) and 8 gm per 20 gm of famotidine (Example 11). Mizumoto does not describe specific use of glycyrrhizin with famotidine, nor disclose an amount of glycyrrhizin to be used in the formulations. Furthermore, Mizumoto is not restricted to use of active agents containing nitrogen-containing moieties, but also describes active agents that do not have nitrogen atoms. For instance, the anti-inflammatory compound cortisol is a steroid that does not have a nitrogen atom.

In light of the standard given above for establishing a case of *prima facie* obviousness, Mizumoto is fatally insufficient to support a case of *prima facie* obviousness. Mizumoto does not teach or suggest each and every element of the claimed compositions because there is nothing in Mizumoto on the use of glycyrrhizin in an amount sufficient to form a complex with a nitrogen containing active agent to generate a compositions substantially free of uncomplexed active agent. Mizumoto is void of any teaching for any specific amount of glycyrrhizin other than a general description for its use as a sweetener.

Moreover, as with Zyck, Mizumoto provides no motivation or suggestion to arrive at the claimed compositions. Mizumoto is limited to use of glycyrrhizin as an artificial sweetener and does not point to any advantage or desirability of using glycyrrhizin over any of the other listed artificial sweeteners nor cite any advantage or desirability of selective use of glycyrrhizin specifically with nitrogen containing active agents as opposed to other active agents that do not contain a nitrogen atom (*e.g.*, steroidal anti-inflammatory compounds). Because Mizumoto limits the use of glycyrrhizin as an artificial sweetener, which typically constitute a minor fraction of the total weight of a pharmaceutical composition, Mizumoto actually teaches away from the instantly claimed compositions.

Finally, Mizumoto fails to support a reasonable expectation of success. As applicants have emphasized herein, Mizumoto restricts the use of glycyrrhizin as an artificial sweetener and thus does not describe selective use of glycyrrhizin specifically with a nitrogen containing active agent. Thus, a skilled artisan reading the Mizumoto disclosure would not only use glycyrrhizin in amount insufficient to form a composition substantially free of uncomplexed active agent, but the selection of an active agent with a nitrogen containing moiety would be left to chance rather than based on any advantage or desirability of the combination. For these reasons, a skilled artisan following the guidance of Mizumoto would not have a reasonable expectation of success in arriving at the claimed compositions.

Hence, the deficiencies in Mizumoto cannot sustain a *prima facie* case of obviousness. Like the rejection over Zyck, the rejection over Mizumoto is in error, and withdrawal of the rejection is respectfully requested.

Rejoinder of Withdrawn Claims

Claims 6-9 and 17-44 have been withdrawn from further examination as being drawn to non-elected inventions. Claim 1 is a generic claim directed to compositions comprising a complex of glycyrrhizin and active agent with a nitrogen-containing moiety. If a generic claim is found allowable, applicants are entitled to, in addition to the elected species, a reasonable number of species under 37 C.F.R. §1.146 and M.P.E.P. §809.02(c). Accordingly, applicants respectfully request rejoinder of claims 6-9 directed to compositions comprising glycyrrhizin complexed to active agents other than famotidine if claim 1 is determined to be allowable.

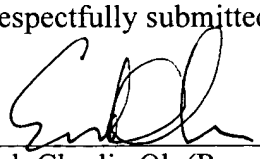
Furthermore, claim 17 is a linking claim that links the claims of inventive Group I to the claims of inventive Group II. As provided in M.P.E.P. §809, a linking claim must be examined with the invention elected, and should any linking claim be found allowable, any restriction requirement issued thereon should be withdrawn and claims directed to the non-elected inventions previously withdrawn from consideration be rejoined and fully examined on their merits for patentability. Accordingly, applicants respectfully request examination of claim 17, and if found allowable, the rejoinder and examination of claims 18-44.

Conclusion

Claims 1-44 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early notification of the same is kindly solicited. If the Patent Office believes that there are further unresolved issues, applicants encourage the Patent Office to contact the undersigned attorney with any questions or concerns by telephone at 415.262.4504.

No fees beyond those submitted herewith are believed due. However, the Commissioner is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (**Order No. 366325-503US (327978)**).

Respectfully submitted,



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Under 37 C.F.R. § 1.34

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